three complementarity determining regions (CDR1, CDR2 and CDR3) of a heavy chain variable region of the amino acid sequence set forth below" can be found in the subject application on page 14, lines 8-24, for example. Support for the particular amino acid sequences of the light chain CDRs can be found in the amino acid sequence of the mouse Act-1 light chain variable region ("Act-1.vl") (SEQ ID NO:12) in Figure 7 of the specification, for example. Support for the particular amino acid sequences of the heavy chain CDRs can be found, for example, in the amino acid sequence of the mouse Act-1 heavy chain variable region ("Act-1.vh") (SEQ ID NO:15) in Figure 9 of the specification. Support for the phrase "an amino acid sequence substantially the same as the amino acid sequence such that the antibody specifically binds to the $\alpha 4\beta 7$ integrin" can be found, for example, on page 14, lines 12-24 and on page 16, lines 17-20.

Claims 23 and 27 have been amended to further clarify that the "functional portion" of the light or heavy chain variable region amino acid sequence shown in Figures 7 and 9, respectively, has binding specificity for $\alpha 4\beta 7$ integrin. Support for this amendment can be found in the specification at page 20, line 33 - page 21, line 1, for example.

Affirmation of election

Applicants' Attorney affirms the election to prosecute the invention of Group I, Claims 1-15, 18-20, 23, 24, 27 and 28, made in a telephone conversation with Examiner Rabin and David Brook on June 2, 1997 in response to the restriction requirement.

Rejection of Claims 1-7, 23, 24, 27 and 28 under 35 USC § 112, first paragraph

Claims 1-7, 23, 24, 27 and 28 are rejected under 35 USC § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable

one skilled in the art to make and use the invention. The Examiner states that the specification does not enable one of skill in the art to "select for the claimed 'at least a portion of' or 'at least a functional portion of' of [sic] the recited immunoglobulin molecules and particular sequences" (Office Action, page 4, lines 9-12). It is the Examiner's opinion that "the specification does not teach how to make functional immunoglobulin comprising portions of the particular sequences disclosed in the specification" or "how to use them commensurate in scope with the claimed invention" (Office Action, page 4, lines 12-15). The Examiner states that the problem of predicting protein structure from mere sequence data of a single protein and "utilizing predicted structural determinations to ascertain functional aspects of the protein are well outside the realm of routine experimentation" (Office Action, page 4, lines 22-25). Citing Rudinger as an indicator of the state of the art of peptide chemistry, the Examiner further states that it is unpredictable whether any of the claimed portions would be active in the instant protein. In conclusion, the Examiner states that due to "the lack of predictability of the art to which the invention pertains and the limited working examples, the state of the prior art, the lack of guidance in the specification and the breadth of the claims, it would take undue experimentation to practice the invention as broadly claimed and this is not sanctioned by the statute" (Office Action, page 5, lines 17-21).

Applicants respectfully disagree. The specification clearly provides guidance for those of skill in the art for making the claimed functional humanized immunoglobulin having binding specificity for $\alpha 4\beta 7$ integrin comprising portions of the particular sequences disclosed in the specification, and using the portions commensurate in scope with the claimed invention.

The phrase "at least a functional portion" appears in Claims 23, 24, 27 and 28 and refers to functional portions of the amino acid sequences of the mouse Act-1 light chain variable region (SEQ ID NO: 12) and the mouse Act-1 heavy chain variable region (SEQ ID NO: 15). In the specification as filed, Applicants define the term "functional portion" as "a portion sufficient for antigen binding of a humanized immunoglobulin which comprises said chain" (specification, page 20, line 33 - page 21, line 1). Applicants have provided a working example wherein functional portions (i.e., the CDR1, CDR2 and CDR3 regions) of the mouse Act-1 light chain variable region amino acid sequence shown in Figure 7 and functional portions (i.e., the CDR1, CDR2 and CDR3 regions) of the mouse Act-1 heavy chain variable region amino acid sequence shown in Figure 9 were grafted onto selected human variable regions to create humanized Act-1 immunoglobulin reactive with $\alpha 4\beta 7$ integrin. Further guidance is provided in the specification wherein Applicants teach that in the embodiment in which the antigen binding region of the humanized immunoglobulin comprises a CDR of non-human origin,

> the humanized immunoglobulin having binding specificity for $\alpha 4\beta 7$ integrin comprises at least one CDR of nonhuman origin. For example, CDRs can be derived from the light and heavy chain variable regions of immunoglobulins of nonhuman origin, such that a humanized immunoglobulin includes substantially heavy chain CDR1, CDR2 and/or CDR3, and/or light chain CDR1, CDR2 and/or CDR3 from one or more immunoglobulins of nonhuman origin, and the resulting humanized immunoglobulin has binding specificity for $\alpha 4\beta 7$ integrin (specification, page 14, lines 8-19).

Clearly, Applicants' specification enables one of skill in the art to select for "at least a functional portion" of SEQ ID NO: 12 and SEQ ID NO: 15 to create a humanized immunoglobulin having binding specificity for $\alpha 4\beta 7$ integrin. However, in order to more particularly point out and distinctly claim the

subject matter which Applicants regard as their invention, Claims 23 and 27 have been amended to indicate that the "functional portion" of the light or heavy chain variable region amino acid sequence shown in Figures 7 and 9, respectively, has binding specificity for $\alpha 4\beta 7$ integrin.

The phrase "at least a portion" appears in Claim 1 and refers to portions of an amino acid sequence(s) of human origin encoding immunoglobulin regions other than the antigen binding region (e.g., the framework regions, the J region, the D region, the constant region). Applicants provide a working example wherein portions (i.e., framework regions) of two different human immunoglobulins (i.e., the human GM 607'CL light chain; the human 21/28'CL heavy chain) were obtained and the CDRs of the murine anti-Act-1 antibody were grafted onto these human framework regions to create a reshaped human anti-Act-1 variable region. As indicated in the specification, DNA sequences encoding these reshaped human Act-1 variable regions were constructed and joined to DNA sequences encoding human constant regions, other "portions" of a human immunoglobulin (specification, page 32, lines 10-13).

Applicants teach that the human portion of the humanized immunoglobulin can be derived from any suitable human immunoglobulin or immunoglobulin chain (e.g., a constant region or portion thereof can be derived from the κ or λ chains, and/or the γ, μ, α, δ or ϵ heavy chains or human antibodies, including allelic variants) and provide specific examples of portions of human immunoglobulins which can be used to create the claimed humanized antibodies (see specification, page 14, line 25 - page 16, line 35)). For example, Applicants teach that a particular constant region can be selected "in order to tailor effector function" (specification, page 14, lines 33-35). Applicants also teach that the humanized immunoglobulin can include "at least one of the framework regions (FR) derived from one or more chains of an antibody of human origin. Thus, the FR can include a FR1

and/or FR2 and/or FR3 and/or FR4 derived from one or more antibodies of human origin (e.g., from a human immunoglobulin chain, from a human consensus sequence)" (specification, page 16, lines 3-11).

It is routine in the art to obtain immunoglobulins comprising a portion of the constant region using, for example, the papain enzyme. In addition, Applicants provide ample guidance in the specification of methods which can be used to obtain the immunoglobulin portions for use in the invention (specification, page 18, line 6 - page 19, line 12). Finally, Applicants provide guidance regarding methods suitable for assessing the ability of the resulting humanized immunoglobulin to specifically bind $\alpha 4\beta 7$ integrin (see specification, page 17, line 22 - page 18, line 5), and a detailed exemplification (see Example 4 (B), Affinity, page 103, line 13 *et seq.*).

The Examiner states that it is unpredictable whether any of the claimed portions would be active in the instant protein and cites Rudinger as evidence that the state of the art of peptide chemistry is unpredictable. However, the Rudinger article is directed to peptide hormones and does not mention immunoglobulins. Moreover, with respect to the determination of enablement, it is not whether a particular method or technique entails some unpredictability; rather, the focus of the analysis is whether or not the particular method or technique requires undue experimentation. With Applicants' teaching in hand regarding the sequence of novel CDRs having binding specificity for $\alpha 4\beta 7$ integrin and their associated framework regions, the extensive guidance and exemplification provided regarding humanization and the assessment of the resulting antibodies, one of ordinary skill is fully enabled to practice the full scope of the claimed invention. Persons skilled in the art are prepared to construct humanized antibodies and assess their binding specificity for $\alpha 4\beta 7$ integrin as taught by Application. In this regard, the

Examiner's attention is directed to the case of *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), wherein Appellants claimed a method of using a monoclonal antibody having a particular binding specificity for a hepatitis B-surface antigen (anti-HBsAg antibodies). The claims were rejected under 35 USC § 112, first paragraph by the Patent Office on the grounds that production of the claimed antibodies was unpredictable and unreliable, thus requiring undue experimentation. However, the court reversed the rejection stating that:

> In order to determine which anti-HBsAg antibodies satisfy all of the limitations of appellants' claims, the antibodies require <u>further screening</u> to select those which have an IgM isotype and have a binding affinity constant of at least 10^9M^{-1} (*In re Wands*, 8 USPQ2d 1400, 1405 (Fed. Cir. 1988) (emphasis added).

As in the present case, the screening techniques needed to practice the *Wands* invention were well known in the art. Thus, the court further stated that:

> Wands' disclosure provides considerable direction and guidance on how to practice their invention and presents working examples. There was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known (*Id.* at 1406).

As in the *Wands* case, Applicants have provided considerable direction and guidance, including the sequences of particular CDR sequences needed to create a humanized immunoglobulin having binding specificity for $\alpha 4\beta 7$ integrin, and have provided detailed working examples of the claimed immunoglobulins. Additionally, with respect to assessing specificity there was a high level of skill in the art at the time when the present application was filed, and methods needed to practice the invention were well known. In view of the foregoing, it is respectfully submitted that Applicants have provided an enabling disclosure in compliance with 35 USC § 112, first paragraph.

Rejection of Claims 1-7, 23, 24, 27 and 28 under 35 USC § 112, second paragraph

Claims 1-7, 23, 24, 27 and 28 are rejected under 35 USC § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner states that Claims 1-7 are indefinite for reciting "portion of" because the relevant portion have not been identified, and for reciting "at least a portion of" because it is unclear how much of the peptide is required.

35 USC § 112, second paragraph requires that the claims "set out and circumscribe a particular area with a reasonable degree of precision and particularity" (*In re Moore*, 169 USPQ 236, 238 (CCPA 1971)). The statute does not require the description of the invention to be in terms of exact measurement (*U.S. Philips Corp. v. National Micornetics Inc.* 188 USPQ 662, 667 (Distr. Ct. S.D.N.Y. 1976)). Claim 1 clearly indicates that the CDRs are of nonhuman origin. Thus, portions of human immunoglobulins for use in the claimed invention include, for example, the constant region, the framework region, the J region and/or the D region of a human immunoglobulin. As discussed above, Applicants have provided specific working examples of relevant portions of immunglobulins of human origin for use in the claimed invention, and using Applicants' specification as a guide a person of skill in the art is able to identify additional relevant portions of human immunoglobulins into which can be grafted the specific CDRs which have binding specificity for $\alpha 4\beta 7$ integrin. As to how much of a portion of a human immunoglobulin is needed, the claims clearly recite that the resulting humanized immunoglobulin has binding specificity for $\alpha 4\beta 7$ integrin. Using Applicants' disclosure and routine methods, a person of skill in the art can obtain such portions of a human immunoglobulin, and prepare immunoglobulins comprising CDRs of nonhuman origin and the human

immunoglobulin portion(s), and assess whether the resulting humanized immunoglobulin has binding specificity for $\alpha 4\beta 7$.

It is unclear whether Claims 23, 24, 27 and 28 have been rejected under 35 USC § 112, second paragraph, as the Examiner has provided no reason for rejecting these claims. However, Applicants will assume in responding to the rejection that Claims 23, 24, 27 and 28 are rejected under 35 USC § 112, second paragraph due to recitation of the phrase "at least a functional portion of."

With respect to the recitation of "at least a functional portion" of SEQ ID NO:12 or SEQ ID NO:15 (see Claims 23, 24, 27 and 28), independent Claims 23 and 27 have been amended to indicate that the "functional portion" of the light or heavy chain variable region amino acid sequence shown in Figures 7 and 9, respectively, has binding specificity for $\alpha 4\beta 7$ integrin. Thus, the claimed portions of the recited sequences are those which confer binding specificity for $\alpha 4\beta 7$ integrin. As amended, these claims set out and circumscribe a particular area with a reasonable degree of precision and particularity in accordance with the statute.

Rejection of Claims 1-15, 18-20, 23, 24, 27 and 28 under 35 USC § 103(a)

Claims 1-15, 18-20, 23, 24, 27 and 28 are rejected under 35 USC § 103(a) as being unpatentable over Queen *et al.* (U.S. Patent No. 5,530,101) in view of Lazarovits *et al.* (*J. Immunol.*, *151*:6482-6489 (1993)). The Examiner states that "Queen *et al.* teach humanized immunoglobulin (Ig) chains having one or more complementarity determining regions (CDRs) from a donor Ig and a framework region from a human Ig" (Office Action, page 6, lines 25-28). Noting that Queen *et al.* do not teach humanized antibodies having binding specificity for $\alpha 4\beta 7$, specifically humanized Act-1, the Examiner cites Lazarovits *et al.* as teaching Act-1 mAb and that the antigen recognized by Act-1 is $\alpha 4\beta 7$. The Examiner

states that Lazarovits *et al.* teach that interference with $\alpha 4\beta 7$ "may be beneficial in the immunotherapy of rheumatoid arthritis" and Queen *et al.* teach that "any antibody can be humanized" (Office Action, page 8, lines 4-9). The Examiner concludes that:

> [I]t would have been *prima facie* obvious to a person of skill in the art at the time the invention was made to be motivated to use the methods of Queen and the mAb taught by Lazarovits *et al.* to make a humanized Act-1 antibody including fragments, multimers, fusion proteins and conjugates, with the expectation that an antibody would be successfully obtained and useful for therapeutic treatment, for diagnostic assays, and for purifying ligand (Office Action, page 8, lines 15-21).

It is the Examiner's opinion that one of skill in the art would have a reasonable expectation of success in producing the claimed antibodies based on the teachings of the references.

Applicants respectfully disagree. Queen *et al.* describe the design of genes for humanized anti-Tac antibodies which react with the IL-2 receptor; mikβ1 humanized light and heavy chains which together bind to the p75 chain of the IL-2 receptor; Fd79 and Fd138-80 humanized light and heavy chains which respectively bind to the gB and gD glycoproteins of herpes simplex virus; M195 humanized light and heavy chains which together bind to the CD33 antigen; and CMV5 humanized light and heavy chains which together bind to the gH glycoprotein of cytomegalovirus. In addition, Queen *et al.* teach AF2 human-like light and heavy chains. As noted by the Examiner, Queen *et al.* do not teach humanized immunoglobulins having binding specificity for $\alpha 4\beta 7$ integrin (Office Action, page 8, lines 4-5).

Lazarovits *et al.* "investigated the expression of $\alpha 4\beta 7$ in the three compartments of rheumatoid arthritis, the peripheral blood, synovial fluid, and synovial membrane, utilizing the FACS and immunoperoxidase microscopy of frozen tissues" using the murine Act-1 antibody (Lazarovits *et al.*, abstract).

Lazarovits *et al.* teach that synovial fluid T cells and peripheral blood "showed low and equivalent expression of $\alpha 4\beta 7$" Lazarovits *et al.*, page 6486, column 2). Noting that "$\alpha 4\beta 7$ was strongly expressed on T cells derived from rheumatoid synovium," Lazarovits *et al.* conclude that it "is possible that interference with $\alpha 4\beta 7$ may be beneficial in the immunotherapy of RA" (Lazarovits *et al.*, page 6487, column 1, emphasis added). However, Lazarovits *et al.* provide no means for carrying out such immunotherapy, and clearly do not suggest that monoclonal antibody Act-1 should be used for this purpose.

In contrast, Applicants selected the Act-1 antibody having binding specificity for $\alpha 4\beta 7$ integrin, isolated DNAs encoding the rearranged light and heavy chain variable regions from the Act-1 hybridoma, determined the DNA and amino acid sequences of the light and heavy chains, including the sequences of the CDRs and associated framework regions, and designed and prepared humanized immunoglobulins. The instant invention pertains to humanized antibodies comprising either the novel CDRs found by Applicants or CDRs which are substantially the same in sequence such that the antibody specifically binds to $\alpha 4\beta 7$ integrin. In order to expedite prosecution, the claims have been amended to clearly indicate that the claimed humanized immunoglobulins having binding specificity for $\alpha 4\beta 7$ integrin comprise an antigen binding region and at least a portion of a human immunoglobulin, wherein the antigen binding region of the humanized immunoglobulin comprises at least one of three complementarity determining regions (CDR1, CDR2 and CDR3) of a light chain variable region and at least one of three complementarity determining regions (CDR1, CDR2 and CDR3) of a heavy chain variable region of a particular amino acid sequence or an amino acid sequence substantially the same as the particular amino acid sequence such that the antibody specifically binds to the $\alpha 4\beta 7$ integrin.

Where the claimed invention is rejected as obvious in view of a combination of references, § 103 requires both (1) that "the prior art would have suggested to the person of ordinary skill in the art that they should . . . carry out the claimed process"; and (2) that the prior art should establish a reasonable expectation of success (*In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991)). "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." *Id.* There is no particular teaching in the art cited directing the skilled man to select Act-1 antibody for humanization. With respect to motivation, the Examiner states that one would be motivated to make Applicants' claimed invention "because of Queen's teachings of the advantages of humanizing antibodies and the teachings of Lazarovits *et al.* indicating its importance" (Office Action, page 8, lines 21-23). However, Lazarovits *et al.* does not indicate the importance of Act-1 in immunotherapy of RA. Rather, Lazarovits *et al.* emphasizes the "possible" benefits of "interference with $\alpha 4\beta 7$" in the immunotherapy of RA (Lazarovits *et al.*, page 6487, column 1). Here, the Examiner is employing an impermissible obvious to try standard.

Secondly, there is no teaching or suggestion of the sequences of the light and heavy chains or of the six CDRs of Act-1 antibody, or humanized antibodies having the particular structure and function as claimed, including those which can compete with murine Act-1 for binding to $\alpha 4\beta 7$ integrin (e.g., Claim 9). Thus, the references do not establish the requisite reasonable expectation of success with respect to the *particular* antibodies claimed.

The cited references do not teach the CDR sequences recited in the claims or the full sequence of the light and heavy chain variable regions of Act-1 antibody. As claimed, the invention as a whole is not obvious over the prior art of record, which neither teaches nor suggests that the skilled

man select Act-1 in particular, neither teaches nor suggests the sequences of the light and heavy chains or of the six CDRs of Act-1, and neither teaches nor suggests humanized antibodies having the particular structure claimed.

The fact that possible approaches to isolate nucleic acids encoding light and heavy chains, sequence them, and prepare humanized antibodies based on this information, were known (Queen *et al.*) is an improper basis for rejection of the claims, particularly as amended. In the case of *In re Bell*, the PTO emphasized the similarity between the method by which Bell made the claimed sequences and a method taught by Weissman. However, the court found such reliance to be improper, and held that "[t]he PTO's focus on Bell's method is misplaced. Bell does not claim a method. Bell claims compositions, and the issue is the obviousness of the claimed compositions, not of the method by which they are made" (*In re Bell*, 26 USPQ2d 1529, 1532 (Fed. Cir. 1993) (citing *In re Thorpe*, 227 USPQ 964, 966 (Fed Cir. 1985), for the proposition that "[t]he patentability of a product does not depend on its method of production"). As each of the independent claims refers to novel and nonobvious sequences of the claimed compositions, the Examiner's reliance upon known methodologies to render the claimed invention obvious is improper on this basis also, dictating withdrawal of the rejection.

As noted above, the claimed invention as a whole is not obvious over the prior art of record. The references fail to teach or suggest the claimed invention.

Citation of References

Applicants cited U.S. Patent No. 5,585,089 (Queen *et al.*) as Reference AC on Form PTO-1449. The Examiner has relied upon a second, different Queen *et al.* patent (i.e., U.S. Patent No. 5,530,101) in the rejection under 35 U.S.C. § 103(a). This second patent does not appear to be listed on Form PTO-892, received with the Office Action. Applicants'

Attorney respectfully requests that U.S. Patent No. 5,530,101 to Queen *et al.* be made of record on a Form PTO-892.

CONCLUSION

In view of the amendments and arguments presented, Applicants respectfully submit that the subject application is in condition for allowance. The Examiner is respectfully requested to reconsider the rejections in the Office Action mailed June 6, 1997 and to withdraw them.

If the Examiner feels that a telephone conversation with Applicants' Attorney would be helpful in expediting the prosecution of this case, the Examiner is urged to contact the undersigned at (781) 861-6240.

Respectfully Submitted,

Helen E. Wendler

Helen E. Wendler
Registration No. 37,964
Attorney for Applicants
(781) 861-6240

Lexington, Massachusetts 02173
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